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(54) Title: A MEDICAMENT FOR THE TREATMENT OF METASTASES

(57) Abstract

There is disclosed a medicament for the treatment of hepatic metastases comprising 5-fluoro-2-deoxyuridine entrapped in liposomes, in a pharmaceutically acceptable carrier.

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A MEDICAMENT FOR THE TREATMENT OF METASTASES

This invention concerns a medicament for the treatment of metastases, especially, though by no means exclusively, for the treatment of hepatic metastases of colorectal adenocarcinoma, and method of manufacturing same.

Colorectal adenocarcinoma is a major cause of death in Western societies with over 55,000 deaths per year in the United States and 20,000 deaths per year in Great Britain.

A majority of those deaths are caused by the secondary tumours, or metastases, produced from the primary tumour. In the case of colorectal adenocarcinoma, these metastases tend to form in the liver.

At present, chemotherapy is used to treat the majority of patients with colorectal adenocarcinoma, with 5 Fluoruracil (5-FU) being the drug of choice. However, a major drawback to this therapy is its high toxicity. The major toxicity of 5-FU is myelosuppression. In addition, alopecia is frequently encountered and mucocitis, nausea and vomiting are common.

More recently, a combined therapy of 5-FU and leucovorin has proved more beneficial to patients in efficacy against the metastases of colorectal adenocarcinoma.

However, a major side effect of the combination therapy is severe, life threatening and occasionally fatal diarrhoea since this drug therapy inhibits DNA synthesis of both normal colonic mucosal cells as well as colorectal tumour cells.

Thus an alternative drug delivery system which would by-pass the normal gut mucosal cells but deliver cytotoxic concentrations to hepatic metastases is required.

Liposomes are suitable candidates as liposome-entrapped drugs are taken up by macrophages and monocytes and are delivered through fenestrated endothelium to such organs as liver, spleen and bond marrow following their intravenous injection, thereby reducing systemic toxicity associated with chemotherapeutic drugs.

However, 5-FU does not lend itself well to liposomal entrapment and, additionally, even when delivered to macrophages in liposomes, 5-FU rapidly leaves these cells by osmosis.

The present invention provides a medicament for the treatment of hepatic metastases which overcomes, at least to some extent, the problem aforesaid.

According to the present invention there is provided a medicament for the treatment of hepatic metastases comprising 5-fluoro-2-deoxyuridine entrapped in liposomes, in a pharmaceutically acceptable carrier.

5-fluoro-2-deoxyuridine (Floxuridine, FudR) is an analogue of 5-FU which is more suitable than 5-FU for liposomal entrapment and will remain within the cells to

which it is delivered in liposomes. FUdR also has a shorter plasma half life, probably less than ten minutes, a higher first-pass liver uptake and is less toxic than 5-FU.

FUdR is also a more effective cytotoxic drug, being four times more effective at inhibiting DNA synthesis via inhibition of thmidyl synthetase than 5-FU (The Cancer Chemotherapy Handbook : Eds Fischer, D S and Knobf, M T, 3rd Edition; Medical Publishers Inc, Chicago and London, 1989).

The medicament may also comprise free leucovorin or free leucovorin may be given at the same time as the FUdR-liposomes. This combined therapy, administered systemically, will be cytotoxic to liver tumours whilst protecting colon and other tissues which will not take up the entrapped drug.

Additionally, this combined therapy is anticipated to be a much more effective therapy than the currently used 'gold standard' therapy of free 5-FU and leucovorin, since free FUdR is known to be even more strongly synergistic with leucovorin than is 5-FU (The Cancer Chemotherapy Handbook, 1989).

The medicament may be administered by any route capable of delivering an effective dose of FUdR-liposomes to the liver.

Preferably, the route of administration of FUdR-liposomes is via intravenous injection.

The liposomes may comprise cholesterol, cholesterol sulphate and

phoshatidyl choline, and preferably 50% cholesterol, 5% cholesterol sulphate and 45% phosphatidyl choline.

The pharmaceutically acceptable carrier may comprise 0.9% saline.

The invention also comprises a method of manufacture of FUdR-liposomes for the treatment of hepatic metastases comprising the following steps:

1. Mixing together cholesterol, cholesterol sulphate and phosphatidyl choline
2. Depyrogenation
3. Drying
4. Lyophilisation
5. Addition of aqueous FUdR
6. Filtration
7. Sterilisation
8. Suspension of the resulting FUdR-liposomes in a pharmaceutically acceptable carrier.

An example of this method of manufacture comprises mixing together 90mg of hydrogenated phosphatidyl choline, 10mg of cholesterol sulphate and 40mg of cholesterol. This mixture is then depyrogenated by filtration through glass fibre and cellulose filters and then dried by rotorary evaporation before being lyophilised under high vacuum. An aqueous solution of FUdR (400mg FUdR in 5ml water) is then admixed with the dried liposomes and the final preparation passed through a series of 0.2 micron filters and finally passed through a sterilisation filtration.

This method generally results in an entrapment of FUdR of around 70%. Such FUdR-liposomes have been shown to be stable up to ten weeks with a small leakage of FUdR occurring after that time.

It is envisaged that patients will be given approximately 30mg/kg/day of the above mentioned FUdR-liposomes daily for five days in 0.9% saline via intravenous injection. Leucovorin will also be administered daily at 50mg/m^2 over two hours with the liposomal FUdR given as a bolus dose at the midpoint.

It will be appreciated that it is not intended to limit the invention to the above example only, many variations, such as might readily occur to one skilled in the art being possible, without departing from the scope thereof.

CLAIMS

1. A medicament for the treatment of hepatic metastases comprising 5-fluoro-2-deoxyuridine entrapped in liposomes, in a pharmaceutically acceptable carrier.

2. A medicament according to claim 1 further comprising free leucovorin.

3. A medicament according to either claim 1 or claim 2 wherein the liposomes comprise cholesterol, cholesterol sulphate and phosphatidyl choline.

4. A medicament according to any preceding claim wherein the pharmaceutically acceptable carrier comprises saline or dextrose solution.

5. A method of manufacture of FUdR-liposomes for the treatment of hepatic metastases comprising the following steps;

1. Mixing together cholesterol, cholesterol sulphate and phosphatidyl choline,
2. Depyrogenation
3. Drying
4. Lyophilisation
5. Addition of aqueous FUdR
6. Filtration
7. Sterilisation
8. Suspension of the resulting FUdR-liposomes in a pharmaceutically acceptable carrier

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 94/02506

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/127 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Week 9315 Derwent Publications Ltd., London, GB; AN 93-121261 & JP,A,05 058 879 (TAIHO PHARM CO LTD) , 9 March 1993	1,4,5
Y	see abstract ---	2,3
X	JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 66,no. 07, July 1977 WASHINGTON, DC (US), pages 984-986, S.P. SIMMONS ET AL. 'liposomal entrapment of floxuridine' see the whole document --- -/--	1,4,5

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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5 April 1995	21. 04. 95
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Authorized officer Benz, K

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 108, no. 11, 14 March 1988 Columbus, Ohio, US; abstract no. 87669v, G.L. SCHERPHOF ET AL. 'liposomes in chemo- and immunotherapy of cancer' page 27; column 1; see abstract & LIPIDS, vol. 22,no. 11, 1987 pages 891-896, ---	1,4,5
Y	CHEMICAL ABSTRACTS, vol. 117, no. 5, 3 August 1992 Columbus, Ohio, US; abstract no. 39925q, M. IIGO ET AL. 'in vivo antitumor effects of fluoropyrimidines on colon adenocarcinoma 38 and enhancement by leucovorin' page 34; column 1; see abstract & JPN. J. CANCER RES., vol. 83,no. 4, 1992 pages 392-396, ---	2
Y	EP,A,0 278 465 (KABUSHIKI KAISHA VITAMIN KENKYUSYO) 17 August 1988 see the whole document -----	3

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/GB 94/02506

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-278465	17-08-88	JP-A- 63196510	15-08-88
		DE-A- 3869637	07-05-92
		US-A- 4906477	06-03-90